

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/104487 A3

- (51) International Patent Classification⁷: **C12Q 1/68**
- (21) International Application Number:
PCT/CA2003/000820
- (22) International Filing Date: **6 June 2003 (06.06.2003)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
60/386,818 **6 June 2002 (06.06.2002)** **US**
- (71) Applicant (*for all designated States except US*): **CEN-
TRE FOR ADDICTION AND MENTAL HEALTH**
[CA/CA]; 33 Russell Street, Toronto, Ontario M5S 2S1
(CA).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **PETRONIS, Arturas**
[CA/CA]; 250 College Street, Toronto, Ontario M5T 1R8
(CA).
- (74) Agents: **GOWLING LAFLEUR HENDERSON LLP et
al.**; 160 Elgin Street, Suite 2600, Ottawa, Ontario K1P 1C3
(CA).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— *with international search report*
- (88) Date of publication of the international search report:
8 April 2004
- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: DETECTION OF EPIGENETIC ABNORMALITIES AND DIAGNOSTIC METHOD BASED THEREON

(57) Abstract: The present invention provides a method of detecting an epigenetic abnormality associated with a disease. The method comprises identifying, within a eukaryotic genome, a locus having a hypomethylated sequence specific for the disease and an endogenous multi-copy DNA element. The method can also comprise separate steps of identifying a disease-specific hypomethylated sequence and identifying an endogenous multi-copy DNA element, where the steps may be performed in any order, so long as a locus is identified that has both a disease-specific hypomethylated sequence and an endogenous multi-copy DNA element. The disease-specific hypomethylated sequences detected in accordance with the present invention indicate putative regions of epigenetic dys-regulation and indicate aberrantly regulated nucleic acid sequences that may cause or predispose a patient to disease, such as, but not limited to, Huntingdon s disease, cancers, diabetes, schizophrenia, or bipolar disorder.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 93/00820

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, EMBL, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>QU GUANG-ZHI ET AL: "Satellite DNA hypomethylation vs. overall genomic hypomethylation in ovarian epithelial tumors of different malignant potential" MUTATION RESEARCH, vol. 423, no. 1-2, 25 January 1999 (1999-01-25), pages 91-101, XP002265794 ISSN: 0027-5107 abstract page 92, right-hand column, paragraph 2 page 94, right-hand column, paragraph 2 -page 97, left-hand column, paragraph 1 page 98, left-hand column, paragraph 2 table 1</p> <p style="text-align: center;">--- -/--</p>	1-4,7,10

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 December 2003

Date of mailing of the international search report

14/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ulbrecht, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00820

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BURMAN ROBERT W ET AL: "Hypomethylation of an expanded FMR1 allele is not associated with a global DNA methylation defect"</p> <p>AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 5, November 1999 (1999-11), pages 1375-1386, XP002265795 ISSN: 0002-9297 abstract page 1378, left-hand column, paragraph 4 -page 1379, right-hand column, paragraph 1</p>	1-4,7,10
X	<p>MINIOU PIERRE ET AL: "Alpha-Satellite DNA methylation in normal individuals and in ICF patients: Heterogeneous methylation of constitutive heterochromatin in adult and fetal tissues"</p> <p>HUMAN GENETICS, vol. 99, no. 6, 1997, pages 738-745, XP002265796 ISSN: 0340-6717 abstract page 741, left-hand column, paragraph 3 -page 742, right-hand column, paragraph 4 table 1</p>	1-4,7,10
X	<p>PETRONIS A ET AL: "Polyglutamine-containing proteins in schizophrenia: An effect of lymphoblastoid cells?"</p> <p>MOLECULAR PSYCHIATRY, vol. 5, no. 3, May 2000 (2000-05), pages 234-236, XP009023130 ISSN: 1359-4184 the whole document</p>	1-4,7,10
X	<p>LIU WEN-MAN ET AL: "Alu transcripts: Cytoplasmic localisation and regulation by DNA methylation"</p> <p>NUCLEIC ACIDS RESEARCH, vol. 22, no. 6, 1994, pages 1087-1095, XP001156938 ISSN: 0305-1048 figure 5</p>	22
A	<p>FLORL A R ET AL: "DNA methylation and expression of LINE-1 and HERV-K provirus sequences in urothelial and renal cell carcinomas"</p> <p>BRITISH JOURNAL OF CANCER, vol. 80, no. 9, July 1999 (1999-07), pages 1312-1321, XP002265797 ISSN: 0007-0920 the whole document</p>	1-19, 21-24

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/CA 03/00820

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 20 (completely) and 22 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20 (completely) and 22 (partly)

Present claims 20 and 22 are formulated as "reach-through" claims. The compounds according to said claims are defined by a method of identification as defined by claims 19 and 21, respectively. However, it is not possible to determine which compounds are covered by such a definition. Consequently, the scope of said claims is not clear (Art. 6 PCT).

The only disclosed instances of compounds falling within the scope of claim 22 are probes consisting of any of SEQ ID Nos. 6-263. As regards claim 20, no genes are disclosed which are located in the vicinity of a hypomethylated endogenous DNA element and display an epigenetically altered expression. The present application only teaches genes which are located close to hypomethylated Alu sequences and does not contain any teaching as to their expression.

Finally, even if claim 22 were analysed taking into consideration only SEQ ID Nos. 6-263, the claim would refer to 258 different probes and therefore lack conciseness (Art. 6 PCT).

Consequently, the search has been carried out for those parts of the claims which appear to be clear and concise, namely those parts of claim 22 relating to the probes consisting of SEQ ID Nos. 6-15. For the above reasons claim 20 could not be searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.